Remarks

Applicants have canceled Claims 1 and 2. Claim 3 has been amended to narrow the claim to the most preferred range of solvents. Support for the amendment may be found in the specification on page 13, line 12. Claim 3 is narrowed by the amendment; therefore, no additional literature search should be required. Applicants submit that no additional fees are incurred by the amendments. Applicants courteously request entry of the amendments.

35 U.S.C. §103

Claims 1-19 stand rejected because the presently claimed compounds and process are allegedly patentably obvious in light of the prior art. Applicants submit that the presently claimed compounds are both different "in kind" and provide surprising, significant beneficial properties not suggested by the prior art.

Applicants submit that the artisan would not be motivated to prepare the claimed salts in light of the startling number of common acids failing to provide the desired stable crystalline salts of Formula 4, as claimed in Claim 4. The Examiner properly points out that In re Cofer, 148 USPQ 268 (CCPA 1966) stated that merely changing the form, purity, or characteristic of an old compound does not render the claimed compound patentable. However, Cofer held that the obviousness determination must include an evaluation of the invention as a whole. Applicants submit that the compounds of Claim 4 are patentably non-obvious when the invention and the pertinent facts are considered as a whole.

Applicants maintain that the compounds of Claim 4, like the crystalline compounds Cofer, are patentable in light of the "subject matter as a whole". *Ibid.* at 271. Salt formation can be an individualistic effect. Berge, Journal of Pharmaceutical

Sciences, **66**:1 (1977) states "Various salts of the same compound often behave quite differently because of the physical, chemical, and thermodynamic properties they impart to the parent compound." Applicants have discovered that the generic teaching of U. S. Patent 5,250,542 (Cantrell) does not, in fact, provide or suggest a means for preparing the stable crystalline pharmaceutically acceptable salts now provided by Claim 4 (Formula 4). The three crystalline salts of Claim 4 are the only three stable crystalline salts the Formula 4 compound known to Applicants. Further, the hydrochloride acetone monosolvate, malate, and sesquimalate of Formula 4 are not generically described or illustrated by example in Cantrell. As stated in Applicants' specification on page 15, lines 23-28, fifteen other common acids failed to provide stable crystalline salts. In light of the startling number of common acids failing to provide the desired stable crystalline compound, Applicants submit that the invention as a whole is not obvious. This invention places the three stable crystalline salts of Formula 4 in the hands of the public for the first time. Therefore, Applicants submit that when the invention is considered as a whole using the criteria set forth in Cofer, the rejection under 35 U.S.C. 103 should properly be withdrawn with regard to Claims 4-10.

The new dihydrate of formula 5 is a compound differing "in kind" from the teachings of Cantrell. The dihydrate compound was neither disclosed nor suggested by Cantrell. Further, the dihydrate provides a compound having surprising beneficial properties. A successful commercial pharmaceutical product should be available as a stable crystalline solid having consistent form and particle size to assure the required reproducible dissolution rates. The new dihydrate compound of Formula 5, as claimed in Claim 11, provides these required features. The dihydrate is particularly surprising in view of

the prior art teachings which provide only a monohydrate compound. Applicants submit that the skilled artisan would not expect that a dihydrate could be prepared, or that such compound would provide the necessary stable crystalline solid of consistent crystal form and particle size as required for successful pharmaceutical development. Therefore, Applicants submit that the dihydrate provides more than a mere change in purity, or degree. Rather, the dihydrate form provides properties necessary for successful commercial development of a pharmaceutical. For all of these reasons, Applicants submit that the invention of the dihydrate "as a whole" is non-obvious, and the rejection of Claims 11-19 under 35 U.S.C. 103 should properly be withdrawn.

Finally, Applicants maintain that the artisan using skill of the art teachings provided by Cheronis would not expect to prepare a crystalline monohydrate compound of Formula 3. Applicants point out on page 13 of the specification, Table I, that most standard crystallization reagents provide a "gum ball" product. The "gum ball" product is difficult to purify and is highly undesirable for commercial purposes. While Cantrell generically teaches an ethanol crystallization for certain compounds, the compound of Formula 3 was not crystallized by the methanol process. Applicants have discovered that the methanol/water ratio is crucial. Claim 3 has been limited to the narrow range of solvents capable of producing the desired crystalline monohydrate compound. Applicants maintain that the skilled artisan would be frustrated in the crystallization of compounds of Formula 3 in light of the persistent "gum ball" product. The claimed process places this important method for preparing crystalline compounds of Formula 3, suitable for commercial development, into the hands of the public.

Summary

Applicants have canceled Claims 1 and 2.

Applicants maintain that Claim 3 is patentably non-obvious in light of the persistent "gum ball" product resulting from standard crystallizations. Claim 3 has been amended to claim only the crucial range of methanol and water.

Applicants submit that Claims 4-10 are not obvious in light of the startling number of common acids failing to provide the desired crystalline salt. Applicants urge that Claims 4-10 are certainly patentable when the Cofer analysis is applied and the invention is considered as a whole.

Finally, Applicants assert that the dihydrate of Claims 11-19 is a surprising new compound, not suggested by the Cantrell reference. The dihydrate provides the public with a compound exhibiting essential surprising beneficial properties. Therefore, Applicants maintain that the rejection under 35 U.S.C. 103 should properly be withdrawn.

For all of the foregoing reasons, Applicants submit that the rejections under 35 U.S.C. §103 should properly be withdrawn. Applicants respectfully request reconsideration and withdrawal of all rejections, and prompt passage if the case to issue.

Respectfully submitted,

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